Review Article

Association between Apical Periodontitis and Interleukin Gene Polymorphisms: A Systematic Review and Meta-analysis

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Abstract

Introduction: Genetic polymorphisms may result in altered gene expression or functional changes of the encoded molecules and could possibly generate a deficient immunity. Consequently, individuals with specific genotypes could be more susceptible to disease or could present an increase in disease severity. Our study is aimed to verify, through a systematic review and meta-analysis registered in the PROSPERO database (CRD42016043905), whether currently available evidence supports a relationship between interleukin gene polymorphisms and apical periodontitis (AP). **Methods:** A broad search for studies was conducted. The following databases were used: PubMed, Scopus, Web of Science, and the Virtual Health Library (MEDLINE, SciELO, IBECS, and LILACS). The Medical Subject Headings (MeSH) terms "Periapical Periodontitis," "Periapical Abscess," "Polymorphism, Genetic," and "Polymorphism, Single Nucleotide" were used. MeSH synonyms, related terms, and free terms were included. After application of the eligibility criteria, selected studies were qualified by assessment of their methodologic quality. A fixed effects model was used for the meta-analysis. **Results:** The initial search identified 71 references. After excluding duplicate abstracts, 33 were selected. From these, 6 were eligible for quality assessment; 5 were classified as being of moderate quality, and 1 was classified as being of high quality. **Conclusions:** From these included studies, polymorphisms in *IL1B*, *IL6*, and *IL8* were associated with AP. Polymorphisms in *IL1A*, *IL10*, or *IL12B* were not associated with AP regardless of the methodology used. The meta-analysis suggested that the genotype and allele distribution of *IL1B* (+3954 C/T) gene polymorphism was different in post-treatment AP. More research in this area is warranted to confirm these results. *(J Endod 2017;■:1–8)*

Key Words

Genetic, interleukin, periapical abscess, periapical periodontitis, polymorphism

Significance

The presence of microorganisms, host risk factors, and genetic background are determining factors in the pathogenesis of apical periodontitis. Recent investigations have focused on the identification of genetic polymorphisms involved in different aspects of the host response.

Apical periodontitis (AP) is generally a sequel of root canal infection (1), but even though microorganisms play the principal role in the etiology of AP, the presence of inflammatory cells such as lymphocytes, macrophages, and neutrophils in human periapical lesions shows that the immune response is directly involved in the pathogenesis of the disease (2).

Macrophages and type 1 T helper (Th1) cells were considered to be the principal immunologic constituents of periapical lesions (2,3). Consequently, cytokines such as *interleukin (IL)-1α*, *IL-1β*, *IL6*, *IL8*, and *IL12p40;* tumor necrosis factor (TNF) alpha; and interferon-c can have a potential role in the development of AP (1, 4–6). Interleukins are functional cytokines considered to be the main mediators of the inflammatory response. Their local effects include enhanced leukocyte adhesion to endothelial walls, stimulation of lymphocytes, potentiation of neutrophils, production of prostaglandins and proteolytic enzymes, enhanced bone resorption, and inhibition of bone formation (1).

Recent investigations have focused on the identification of single-nucleotide polymorphisms involved in different aspects of the host response. These investigations also focused on the ability of these polymorphisms to generate a compromised immunity that can contribute to understanding the complex mechanism of diseases (7–12). For instance, it has been reported that the substitution of a cytosine (C) by a thymine (T) in the *IL1A* promoter (rs1800587 position −889) and exon 5 of *IL1B* (rs1143634, position +3954) is related to an increase in IL-1α and IL-1β levels in gingival crevicular fluid (13–15). Hence, genetic factors can influence inflammatory and immune responses in general, and individuals could respond differently to common environmental challenges according to their genetic profiles.

Some investigations have focused on genetic polymorphisms and their association with AP. Therefore, the purpose of this systematic review and meta-analysis was to inves-

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tigate whether currently available evidence supports a relationship between interleukins, genetic polymorphisms, and AP.

Methods

This systematic review was registered in the PROSPERO database (http://www.crd.york.ac.uk/PROSPERO/), CRD42016043905, and was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statements (www.prismastatement.org). The protocol for this was developed based on criteria adopted from published recommendations on the assessment of the quality of genetic association studies (16–18).

Focused Question

The present systematic review was conducted in order to answer the following focused question: "Is there an association between interleukin gene polymorphisms and AP in the permanent teeth of humans?" This question was developed by using the patient population, exposition, comparison, and outcome framework.

Inclusion and Exclusion Criteria

The following article types were considered:

1. Clinical trials, case-control studies, cross-sectional studies, or cohort studies
2. Studies focusing on human beings
3. Studies that evaluated the association between interleukin gene polymorphisms and AP
4. Studies in which genetic polymorphisms were quantified and detailed

Exclusion criteria included the following: duplicate articles, editorial letters, historical reviews, book chapters, theses, guidelines, cell culture laboratory studies, and animal studies. Also excluded were descriptive studies, such as case reports and case series.

Literature Search Strategy

An electronic search was conducted in PubMed, Scopus, Web of Science, and Virtual Health Library (LILACS, IBECS, MEDLINE, and SciELO) databases through March 15, 2016, without year and language restrictions. The gray literature was consulted through OpenGrey (http://www.opengrey.eu). Researchers were contacted to identify additional studies. The Medical Subject Headings (MeSH) terms (www.nlm.nih.gov/mesh/meshhome.html) used in the search were "Periapical Periodontitis," "Periapical Abscess," "Polymorphism, Genetic," and "Polymorphism, Single Nucleotide." Furthermore, we included MeSH synonyms, related terms, and free terms (Table 1). The Boolean operators "AND" and "OR" were applied to combine the key words. The searches were complemented by a manual search of the reference list from the included articles.

Study Selection

Initially, 2 of the authors (A.G.S. and L.A.A.) selected the studies by title and abstracts according to the previously described search strategy. To evaluate agreement between authors, 10% of the publications were randomly selected and had their classification compared, and then a kappa statistic of 0.97 was determined. Only studies that matched the inclusion criteria were accepted. Studies appearing in more than 1 database were considered only once. In those cases in which the abstract and the title were not clear, the study was fully read in order to minimize the possibility of disregarding important studies. Subsequently, the full texts of all potentially eligible studies were accessed, and the inclusion and exclusion criteria were again applied. Any disagreement was discussed and solved by consensus or through discussion with a third author (L.S.A.).

TABLE 1. Search Strategy

PubMed	#1 ("Periapical Periodontitis" [MeSH Terms] OR "Periapical Periodontitis" [Title/Abstract] OR "Periapical Abscess" [MeSH Terms] OR "Periapical Abscess" [Title/Abstract] OR "apical periodontitis" [Title/Abstract]) #2 ("Polymorphism, Genetic" [MeSH Terms] OR "Polymorphism, Genetic" [Title/Abstract] OR "Polymorphism, Single Nucleotide" [MeSH Terms] OR "Polymorphism, Single Nucleotide" [Title/Abstract] OR "Polymorphism" [Title/Abstract] OR "SNP"[Title/Abstract]) #1 and#2
Scopus	#1 (TITLE-ABS-KEY (periapical periodontitis) OR TITLE-ABS-KEY (periapical abscess) OR TITLE-ABS-KEY (apical periodontitis)) #2 (TITLE-ABS-KEY (polymorphism, genetic) OR TITLE-ABS-KEY (polymorphism, single nucleotide) OR TITLE-ABS-KEY (polymorphism) OR TITLE-ABS-KEY (snp)) #1 and#2
WOS	#1 TS=("Periapical Periodontitis" OR "Periapical Abscess" OR "apical periodontitis") #2 TS=("polymorphism, genetic" OR "polymorphism, single nucleotide" OR "polymorphism" OR "snp") #1 and#2
VHL	(tw:(polymorphism genetic OR polymorphism single nucleotide OR polymorphism OR snp)) AND (tw:(Periapical Periodontitis OR Periapical Abscess OR apical periodontitis))

MeSH, Medical Subject Headings; VHL, Virtual Health Library.

Quality Assessment

The authors adapted a 10-point scoring sheet based on criteria from published recommendations on the assessment of the quality of genetic association (16). Each quality criterion was assessed as either "present" (yes, score of 1 point) or "absent or undetermined" (no, score of 0 points). One author initially scored all of the articles. In any article in which the author felt uncertainty about assigning an individual score, the second author independently scored the article, and then a consensus was reached for the final score. Agreement was good (standard deviation of the difference in scores was 0.1). A final quality score was obtained by summation of each component giving a range of 0–10 for each study. Based on the score, the studies were classified into 3 categories:

1. High methodologic quality, presenting 8 or more criteria
2. Moderate methodologic quality, presenting 5 to 7 criteria
3. Low methodologic quality, presenting 4 or fewer of the evaluated criteria

Considering the methodologic quality, the studies were also classified as having high, moderate, or low evidence. Only studies with high or moderate evidence were used in this systematic review.

Data Extraction

The data from the included studies were compiled and organized according to

1. The first author of the article and publication year
2. The population studied and ethnicity
3. Sample size per condition

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